FDA Perspective:
Statistical Considerations for Very Small Clinical Trials

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Outline

- Why a small clinical trial?
- What can we do with limited patients to enroll in the trial?
  - Change the standard (one-sided 0.05)?
- Strategies: More efficient use of the available patients
  - Endpoints
  - Designs

Why a Small Clinical Trial?

- Need adequate evidence of safety and efficacy with limited information
- Rare disease
- Patient population: fewer than 1000
  - Frequently in the 10s to 100s
- Major centers: 100-200 patients
  - Inclusion/exclusion may reduce by 50%
  - Consent issues reduce another 50%
  - Stakeholders may be able to increase numbers

What Can We Do with Limited Patients to Enroll in the Trial?

- Should the FDA apply the same standard (e.g., two-sided 0.05, one-sided 0.025) and hope for a large treatment effect?
- Change the standard?
  - One-sided 0.05 – lower level of evidence
  - Reduce power – smaller n, but greater risk of failed study

What Can We Do with Limited Patients to Enroll in the Trial? (2)

- Strategies: More efficient use of the available patients
  - Endpoints
    - Clinical endpoint (success/fail)
    - Serum/plasma concentration (a surrogate?)
    - Time to event

What Can we do with Limited Patients to Enroll in the Trial? (3)

- Designs
  - Parallel Group (2)
  - Paired – difficult to impossible
  - Crossover – not possible if treatment permanently changes patient

Endpoints

- Continuous vs Binary
  - Tolerance interval – show that a substantial fraction of the values of the variable lies within an acceptable range
    - Serum concentration after treatment is 40% with a 15% s.d.
      - Confidence interval uses $40 \pm 1.96*15/\sqrt{n}$
      - Tolerance interval uses $40 \pm K*15$ where K depends on the confidence and the fraction of the population to be covered. (K >1.96, sometimes by quite a bit)
      - Note that tolerance intervals refer to the population while confidence refers to the mean

Endpoints (2)

- Longitudinal vs fixed time
  - Get multiple measurements from each patient
    - Only works partly – 100 measurements from 2 patients is not the same information as 4 measurements from 50 patients
    - Statistical models
      - GEE – generalized estimating equaiotns
      - Average

An Example

- Thrombotic prevention of TE in at risk ATIII deficient patients (pregnant patients)
  - Clinical endpoint = no TE for each pregnancy. Difficult to generate much data. Case for one arm study to beat a standard
  - Plasma levels of thrombate (typical 120-140 with s.d. about 10).
    - Use tolerance interval to show 95% of population is above 100
    - Use confidence interval to show mean is above 125

Endpoints (2)

- Reduce the measurement error
  - Multiple measurements within relatively short time period – need recurrent problems (e.g., bleeds in hemophilia)
  - Perform replicate assays – cost and facilities are considerations
  - Remember the unit of analysis is the patient, not the visit – 100 visits of 2 patients isn't the same as 4 visits of 50 patients

Endpoints (3)

- Surrogate or alternative endpoint rather than clinical endpoint
  - Plasma level versus success/failute
  - Usually a tighter comparison, but there may be a question of whether this represents a clinical benefit to the patient

Design

- Single arm
  - ICH E10, historical data
    - Compare to a standard, or treat historical data as a pseudo-arm. Most useful when outcome is uniform and known
    - Should be close in time (data from 20 years ago may not be acceptable)
- Parallel vs Crossover
  - Crossover feasible only if the treatment does not cause a permanent change in the patient – e.g. immune status, death

Summary

- Why a small clinical trial?
  - Don’t have suffiicient patients
  - Not don’t want to do a larger trial
- Strategies for more efficient use of the available patients
  - Endpoints – surrogates, PK, etc.
  - Designs – crossover, single arm

Summary (2)

- When the patient population is quite small, we are very limited in the trials we can conduct
- Dichotomous endpoints have relatively low power, so consider continuous variables with small variance
- Consider longitudinal studies and crossover studies when feasible.